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Transition to secondary progression in relapsing-onset multiple sclerosis: Definitions and risk factors

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Abstract

Background: No uniform criteria for a sensitive identification of the transition from relapsing–remitting multiple sclerosis (MS) to secondary-progressive multiple sclerosis (SPMS) are available.

Objective: To compare risk factors of SPMS using two definitions: one based on the neurologist judgment (ND) and an objective data-driven algorithm (DDA).

Methods: Relapsing-onset MS patients ($n = 19{,}318$) were extracted from the Italian MS Registry. Risk factors for SPMS and for reaching irreversible Expanded Disability Status Scale (EDSS) 6.0, after SP transition, were estimated using multivariable Cox regression models.

Results: SPMS identified by the DDA ($n = 2343$, 12.1%) were older, more disabled and with a faster progression to severe disability ($p < 0.0001$), than those identified by the ND ($n = 3868$, 20.0%). In both groups, the most consistent risk factors ($p < 0.05$) for SPMS were a multifocal onset, an age at onset >40 years, higher baseline EDSS score and a higher number of relapses; the most consistent protective factor was the disease-modifying therapy (DMT) exposure. DMT exposure during SP did not impact the risk of reaching irreversible EDSS 6.0.

Conclusion: A DDA definition of SPMS identifies more aggressive progressive patients. DMT exposure reduces the risk of SPMS conversion, but it does not prevent the disability accumulation after the SP transition.

Keywords: Multiple sclerosis, secondary progressive, disease registry, big data, prognosis, data-driven algorithm

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Introduction

To date, secondary-progressive multiple sclerosis (SPMS) is diagnosed retrospectively by neurologists, according to the Lublin definition: a history of a gradual disability progression, independent of relapses, after an initial relapsing course.[1,2] No biological nor clinical markers are available to make more sensitive and reliable the identification of the SP conversion. Thus, it is difficult to establish the exact date of conversion from one course to the other one, mainly because, on a clinical standpoint, the relapsing–remitting (RR) and the SP forms are a continuum of disease with the boundary between them being somewhat indistinct.

Recently, Lorscheider and colleagues[3] proposed an objective definition of SPMS based on the application of an algorithm to the EDSS score evaluations longitudinally recorded in the MSBase platform.

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Most of the studies so far performed to assess the risk factors for SPMS transition have been conducted on clinical cohorts in which the SPMS definition was based on the subjective judgment of the neurologists.[4–7] It is widely accepted that the main risk factors for SPMS are an older age at onset, male gender, an incomplete recovery from the first relapse, and a shorter time to the second relapse.[4–8]

The way the conversion to SPMS is defined might affect the evaluation of risk factors, including the effect of disease-modifying therapies (DMTs), potentially associated with the disease course transition.

Therefore, in this study, we compared the risk factors for the transition from RR to SP course in a large cohort of relapsing-onset MS prospectively followed up in the Italian MS Registry (IMSR), using two different SPMS definitions: the first was based on the subjective decision made by the treating neurologist,[2] and the second was based on a more recently proposed[3] data-driven algorithm. Risk factors for reaching an irreversible EDSS score 6.0 after the SP transition were also evaluated.

Methods

Standard protocol approvals and patient consents

The IMSR[9] was approved by the ethical committee at the "Azienda Ospedaliera/Universitaria—Policlinico of Bari" (Study REGISTRO SM001—approved on 08/07/2016) and by local ethics committees in all participating centers. Patients signed an informed consent that allows to use clinical data for research purposes. This study is retrospective, non-interventional, with a secondary data use.

Study population

Data extraction was performed by applying manually sequential filters to the data set in September 2018. A cohort of relapsing–remitting multiple sclerosis (RRMS) patients with at least 5 years of follow-up and with at least three EDSS scores recorded was selected.

A minimum data set was retrieved including the following variables: date of birth, gender, date of disease onset, onset symptoms, dates of relapses, dates of EDSS evaluations with complete information regarding functional scores (FS), start- and end-dates of all the administered DMTs, and the date of conversion to SPMS assigned by the treating neurologist.

Definitions of SPMS

Two SPMS definitions were used:

1. Neurologist definition (ND): A definition based on the subjective decision made by the neurologists according to the Lublin criteria for SP.[1,2] For this definition, the date of SP conversion, entered by the neurologists in the (iMed®) software, was used.
2. Data-driven algorithm (DDA): An algorithm based on a previous published definition[3] with some modifications: a three-strata progression magnitude (1.5-point increase if the baseline EDSS was 0, 1.0-point increase if the baseline EDSS was 1.0–5.5, 0.5-point increase if the baseline EDSS was >5.5) with a minimum EDSS score of 4.0, and a minimal pyramidal FS score of 2.0 at the time of conversion to SPMS confirmed at 3 months and at the end of follow-up (last EDSS score $\geqslant 4.0$; last pyramidal FS score $\geqslant 2.0$). In order to reduce the impact of transient EDSS modifications due to relapses, all the EDSS scores collected during a relapse (± 30 days) were excluded.

Statistical analysis

Summaries of continuous variables have been calculated as median with interquartile ranges (IQR) or mean and standard deviation (SD); categorical variables have been presented as frequencies (proportions).

Between-group comparisons were performed using the Student test (for continuous variables normally distributed) or the Mann–Whitney test (for continuous variables not normally distributed) or the chi-square test (for categorical variables).

The risk (hazard ratio (HR) and 95% confidence interval (CI)) of transition to SP was estimated using multivariable Cox proportional hazards models. The baseline of this analysis has been set at the time of disease onset.

The models included the following covariates: age at disease onset (0–20, 20–40, >40 years), gender, type of onset (monofocal/multifocal), baseline EDSS score, relapses before SP conversion, treatment exposure duration (as percentage of time spent on active treatment using the quartile distribution), time from disease onset to the first DMT start (using the quartile distribution), and decade of birth.

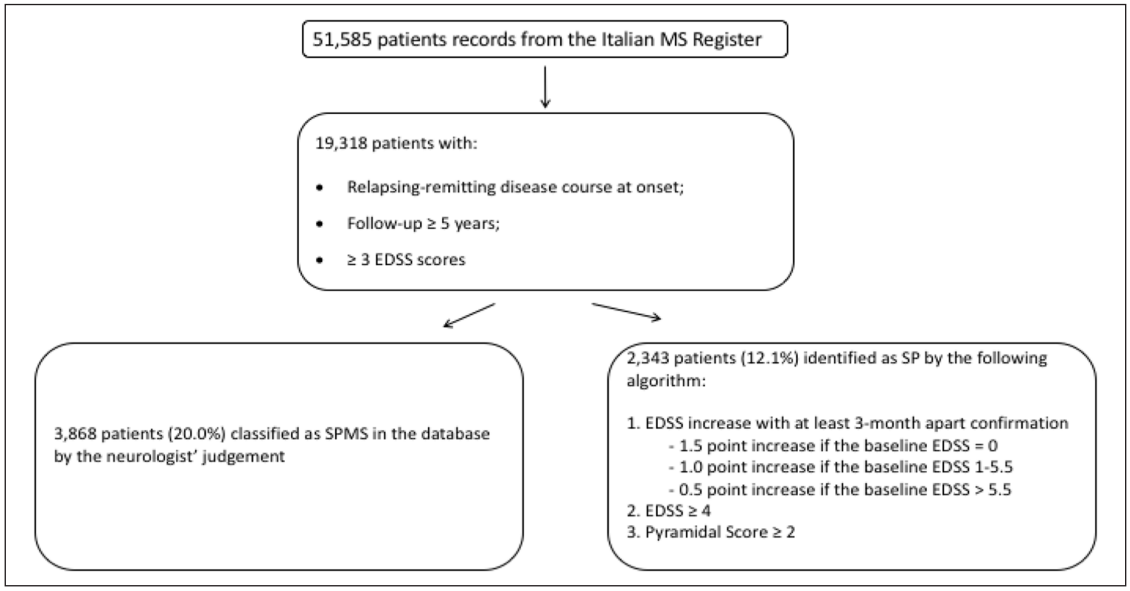

Figure 1. Flow chart of the patient selection from the Italian MS Registry.

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Then, the risk of reaching an irreversible EDSS score of 6.0 after SP transition was estimated using multivariable Cox proportional hazards models in patients converted to SP (according to the two definitions). The baseline of this analysis has been set at the time of SP conversion.

The models included the following covariates: age at disease onset (0–20, 20–40, >40 years), gender, type of onset (monofocal/multifocal), baseline EDSS score at the time of SP conversion, relapses before SP conversion (1, 2, 3, >3), treatment exposure duration before SP conversion (as percentage of time spent on active treatment using the quartile distribution), treatment exposure after the SP conversion (yes/no), disease duration at SP conversion, and decade of birth.

A p value of <0.05 was considered statistically significant. All statistical tests were two-tailed. Analyses were performed using R version 3.2.0.

Results

The final cohort was composed by 19,318 relapsing-onset MS patients, followed for a median (IQR) of 16.6 (11.2–23.5) years. This cohort has been exposed to DMTs for a median (IQR) 71.64 % (34.01–100.00) of the follow-up time. The first DMTs prescribed were injectables (86.8%), azathioprine (8.2%), mitoxantrone (2.4%), new oral DMTs (1.6%), or natalizumab (1.1%), and 2195 patients were never exposed to DMTs during the follow-up.

The flow chart which describes the patients' selection procedure is reported in Figure 1.

A total of 3868 (20.0%) patients were classified as SPMS according to the ND, whereas 2343 (12.1%) were identified as SPMS by applying the DDA.

Table 1 reports the clinical characteristics of patients stratified by the occurrence of the conversion to SPMS according to the two definitions.

At disease onset, patients who converted to SPMS, regardless of the definition used, were older ($p<0.001$), more frequently males ($p<0.001$), had a higher mean EDSS score ($p<0.001$), and a higher frequency of multifocal onset ($p<0.001$) in comparison with patients who did not convert.

Clinical and demographic characteristics of patients at the SPMS conversion and during the subsequent follow-up, according to the two definitions, are reported in Table 2.

In the subgroup of SPMS patients defined according to the ND, the median time (IQR) to conversion was shorter (12.0 (7.0–18.7) vs 15.4 (9.9–22.5) years), the median age at SP was younger (44.0 (37.0–51.0) vs 47.2 (40.2–54.9) years). However, the median EDSS score at SP was the same in both groups (4.5 (3.5–6.0) vs 4.5 (4.0–6.0)), it ranged from 0 to 9.0 in the group identified by the ND and from 4.0 to 9.0 in the group diagnosed using the DDA. The mean (SD) number of

Table 1. Baseline clinical and demographic characteristics of relapsing patients ($n = 19{,}318$) stratified by the occurrence of SPMS according to the neurologist judgment (ND) and the data-driven algorithm (DDA).

Variable	SPMS by the ND			SPMS by the DDA		
	No SPMS	SPMS	*p*	No SPMS	SPMS	*p*
N (%)	15,450 (80.0%)	3868 (20.0%)		16,975 (87.8%)	2343 (12.2%)	
Age at onset, median (IQR)	27.9 (22.3–35.0)	29.5 (23.0–37.5)	<0.0001	28.0 (22.5–35.3)	29.5 (23.0–37.0)	<0.0001
Classes of age at onset, *n* (%)						
0–⩽20	2508 (16.3)	571 (14.8)	<0.0001	2751 (16.2)	328 (14.0)	<0.0001
20–⩽40	10,835 (70.1)	2586 (66.9)		11,822 (69.6)	1599 (68.3)	
>40	2107 (13.6)	711 (18.3)		2402 (14.2)	416 (17.7)	
First EDSS, median (IQR)	1.5 (1.0–2.5)	4.0 (2.5–5.5)	<0.0001	1.5 (1.0–2.5)	3.5 (2.0–5.5)	<0.0001
Sex, *n* (%)						
Female	10,677 (69.1)	2414 (62.4)	<0.0001	11,578 (68.2)	1513 (64.6)	0.0004
Male	4773 (30.9)	1454 (37.6)		5397 (31.8)	830 (35.4)	
Total no. of relapses, median (IQR)	3.0 (1.0–6.0)	3.0 (1.0–7.0)	<0.0001	3.0 (1.0–6.0)	5.0 (2.0–8.0)	<0.0001
Onset symptoms						
Unifocal	13,530 (87.7)	3293 (85.3)	<0.0001	14,849 (87.6)	1974 (84.3)	<0.0001
Multifocal	1900 (12.3)	567 (14.7)		2098 (12.4)	369 (15.7)	

SPMS: secondary-progressive MS; IQR: interquartile range; EDSS: Expanded Disability Status Scale.

Table 2. Clinical and demographic characteristics of SPMS identified by the neurologist judgment (ND) and the data-driven algorithm (DDA).

Variables	SPMS by ND *N* = 3868	SPMS by the DDA *N* = 2343
Time from onset to SP, years, median (IQR), years	12.0 (7.0–18.7)	15.4 (9.9–22.5)
Age at the conversion to SP, median (IQR), years	44.0 (37.0–51.0)	47.2 (40.2–54.9)
No. of relapse before SP conversion, mean (SD)	1.8 (1.2)	1.7 (1.1)
EDSS at the time of SP conversion, median (IQR, range)	4.5 (3.5–6.0, 0–9.0)	4.5 (4.0–6.0, 4.0–9.0)
Follow-up from the onset of SP, years, median (IQR), years	10.4 (6.5–15.0)	5.9 (3.4–9.4)
No. of relapse after SP, mean (SD)	1.5 (2.5)	1.4 (2.3)
Time to EDSS 6.0 from SP, median (IQR), years	3.5 (1.6–7.2)	2.5 (1.5–4.2)
Age at EDSS 6.0, mean (SD), years	46.7 (39.5–54.3)	48.6 (41.6–55.8)

SPMS: secondary-progressive MS; SP: secondary progression; IQR: interquartile range; EDSS: Expanded Disability Status Scale; SD: standard deviation.

relapses after SP transition did not differ between the two groups (1.5 (2.5) vs 1.4 (2.3)), but the median time to reach an irreversible EDSS 6.0 from SP transition was shorter in SPMS patients identified by the DDA than in those defined by treating neurologists (.5 (1.5–4.2) vs 3.5 (1.6–7.2) years).

Only 1514 patients were defined as SPMS by both the definitions. A statistical comparison of the main characteristics at the time of SP conversion of patients uniquely identified as SPMS by the neurologists (2354/3868) or by the DDA (829/2343) confirmed that SPMS identified by the DDA were significantly older ($p < 0.0001$), more disabled ($p < 0.0001$) and with a faster progression to severe disability after the SP transition ($p < 0.0001$), than those identified by the ND.

Risk of conversion to SPMS

The results of the multivariable Cox regression models for estimating factors associated with the conversion

Table 3. Risk factors of SPMS identified according to the neurologist judgment (ND) and the data-driven algorithm (DDA).

Parameter	SPMS by ND ($n=3868$)		SPMS by DDA ($n=2343$)	
	HR (95% CI)	p	HR (95% CI)	p
Female sex	0.77 (0.72–0.82)	<0.0001	0.94 (0.86–1.02)	0.13
Classes of age at onset, <20 reference group				
>40	1.85 (1.63–2.09)	<0.0001	2.26 (1.92–2.67)	<0.0001
20–≤40	1.17 (1.06–1.28)	0.002	1.44 (1.27–1.64)	<0.0001
Type of clinical onset, monofocal reference group				
Multifocal	1.13 (1.03–1.23)	0.011	1.26 (1.12–1.40)	<0.0001
Quartile of the % of FUP spent on DMTs, 1° quartile (Q1) reference group				
Q4			0.22 (0.18–0.26)	<0.0001
Q3	0.53 (0.49–0.58)	<0.0001	0.53 (0.46–0.61)	<0.0001
Q2	0.85 (0.78–0.93)	0.0002	0.76 (0.67–0.86)	<0.0001
Quartile of time to first DMT start, 1° quartile (Q1) reference group (within 1.4 years form onset)				
Q4 (>10.1 years)	0.92 (0.80–1.05)	0.22	0.43 (0.36–0.50)	<0.0001
Q3 (4.4–10.1 years)	1.45 (1.27–1.66)	<0.0001	0.91 (0.77–1.06)	0.22
Q2 (1.5–4.3 years)	1.46 (1.27–1.69)	<0.0001	1.10 (0.93–1.29)	0.27
Baseline EDSS score	1.50 (1.48–1.53)	<0.0001	1.41 (1.38–1.44)	<0.0001
Presence of Relapses before SP (as time-dependent)	1.78 (1.64–1.94)	<0.0001	2.90 (2.54–3.30)	<0.0001
Decade of birth	0.52 (0.47–0.57)	<0.0001	0.89 (0.80–0.99)	0.04

SPMS: secondary-progressive MS; SP: secondary progression; IQR: interquartile range; EDSS: Expanded Disability Status Scale; Q1: first quartile; Q2: second quartile; Q3: third quartile; Q4: fourth quartile.
Quartile of the % of FUP spent on DMTs for the data-driven definition: Q1 < 21.0%, Q2: 21.0%–41.1 %, Q3: 41.2%–73.1%, Q4 > 73.1%.
Quartile of the % of FUP spent on DMTs for the neurologist definition: Q1 < 34.1%, Q2: 34.2%–71.6%, Q3–4 > 71.6%.
Quartile of time to first DMT start from disease onset for both the definitions: Q1 ≤ 1.4 years, Q2: 1.5–4.2 years, Q3: 4.3–10 years, Q4 > 10 years.

to SP phase in each of two SPMS cohorts are reported in Table 3.

In both cohorts, an age at onset >40 years (DDA group: HR (95% CI): 2.26 (1.92–2.67), $p<0.0001$; ND group: 1.85 (1.63–2.09), $p<0.0001$), a multifocal onset (DDA group: 1.26 (1.12–1.40), $p<0.0001$; ND group: 1.13 (1.03–1.23), $p=0.011$), a higher baseline EDSS score (DDA group: 1.41 (1.38–1.44), $p<0.0001$; ND group: 1.50 (1.48–1.53), $p<0.0001$), and a higher number of relapses during the RR phase of the disease (DDA group: 2.90 (2.54–3.30), $p<0.0001$; ND group: 1.78 (1.64–1.94), $p<0.0001$) were associated with a higher risk of SP conversion, whereas a longer exposure to DMTs resulted a significant protective factor against this risk. More in details, the DMT exposure during the RR phase was included as quartile (Q1–4). Due to the different time to conversion to SPMS, the quartile distribution was different in the two cohorts. Both the quartile distributions are reported in Table 3 legend. The longer was the treatment exposure, the lower was the risk of conversion to SPMS during the follow-up (DDA group: 24%–78% decreased risk from Q2 to Q4 in comparison with Q1, $p<0.0001$; ND group: 15% and 47% risk reduction for Q2 and Q3–4, $p=0.0002$ and $p<0.0001$, respectively).

The model based on the ND additionally demonstrated that the female gender (0.77 (0.72–0.82), $p<0.0001$) and the time interval between disease onset and treatment start (included as quartile) were associated with a lower risk of conversion to SPMS. The multivariable model showed that patients belonging to the Q2 and Q3 were at higher risk of conversion to SPMS in comparison with patients who have started earlier the treatment (1.46 (1.27–1.69), 1.45 (1.27–1.66), $p<0.0001$).

Risk of reaching EDSS 6.0 after SPMS transition

The median (IQR) follow-up after SPMS transition was 5.9 (3.4–9.4) years for the those identified by the DDA and 10.4 (6.5–15.0) years for those identified by ND.

Table 4. Risk factors of reaching EDSS 6.0 in SPMS identified by the neurologist judgment (ND) and the data-driven algorithm (DDA).

Parameter	SPMS by the ND		SPMS by DDA	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Female sex	1.00 (0.91–1.10)	0.97	0.96 (0.85–1.08)	0.50
Classes of age at onset [<20 years reference group]				
>40	1.90 (0.60–6.02)	0.27	1.99 (0.27–14.80)	0.50
20–⩽40	2.05 (0.65–6.43)	0.22	2.18 (0.30–15.99)	0.44
Type of clinical onset [monofocal reference group]				
Multifocal	1.05 (0.92–1.19)	0.48	1.02 (0.88–1.19)	0.77
Quartile of the percentage of the follow-up spent on DMTs before SP conversion [1° quartile reference group]				
Q4	–	–	0.95 (0.65–1.40)	0.81
Q3	0.66 (0.59–0.75)	<0.0001	0.82 (0.64–1.05)	0.12
Q2	0.90 (0.80–1.02)	0.09	0.96 (0.79–1.16)	0.64
DMT exposure after SP conversion	0.91 (0.73–1.14)	0.40	0.88 (0.75–1.03)	0.10
Baseline EDSS score at the SP conversion	0.97 (0.93–1.00)	0.08	1.39 (1.24–1.57)	<0.0001
Relapses before conversion to SP				
>3	–	–	0.91 (0.73–1.15)	0.44
3	1.20 (1.07–1.36)	0.003	1.13 (0.95–1.35)	0.18
2	1.04 (0.94–1.16)	0.47	1.02 (0.89–1.18)	0.74
Relapses post-conversion to SP included as time-dependent covariate	1.18 (1.07–1.31)	0.001	1.30 (1.15–1.47)	<0.0001
Disease duration at SP conversion	0.97 (0.96–0.98)	<0.0001	1.00 (0.98–1.01)	0.57
Decade of birth	0.92 (0.80–1.07)	0.28	1.03 (0.86–1.22)	0.77

SPMS: secondary-progressive MS; SP: secondary progression; IQR: interquartile range; EDSS: Expanded Disability Status Scale; Q1: first quartile; Q2: second quartile; Q3: third quartile; Q4: fourth quartile.

At the time of SP conversion, 661 patients in the first group (28.2%) and 1167 in the second group (30.2%) had already reached an irreversible EDSS 6.0 and were excluded from the analysis.

At the time of SP transition, the majority of the patients were receiving injectable DMTs (DDA group: 77.6%; ND group: 73.4%), followed by azathioprine (DDA group: 16.8%; ND group: 20.8%), mitoxantrone (DDA group: 4.6%; ND group: 5.4%), natalizumab (DDA group: 0.7%; ND group: 0.4%), teriflunomide and fingolimod (DDA group: 0.4%; ND group: 0%).

Among patients identified as SPMS by the DDA, an irreversible EDSS 6.0 was reached by 1154 patients (68.6%) after a median time of 2.5 (1.5–4.2) years, whereas in those identified by ND, the outcome was reached by 1882 patients (69.7%) after a median time of 3.5 (1.6–7.2) years.

In both SPMS groups, the persistence of relapse activity after the SP conversion (HR (95% CI): DDA group 1.30 (1.15–1.47), $p < 0.0001$; ND group 1.18 (1.07–1.31), $p = 0.001$) resulted the most consistent risk factor for reaching an irreversible EDSS 6.0, whereas the DMT exposure, after the conversion, did not show any effect on this outcome (DDA group: 0.88 (0.75–1.03), $p = 0.1$; ND group: 0.91 (0.73–1.14), $p = 0.4$) (Table 4).

The EDSS score at the time of conversion to SP was associated with higher risk of reaching an irreversible EDSS 6.0, only in the subgroup defined as SPMS according to the DDA (1.39 (1.24–1.57), $p < 0.0001$; 0.97 (0.93–1.00), $p = 0.08$), whereas relapse activity before the conversion to SPMS (1.20 (1.07–1.36), $p = 0.003$), a longer time to convert to SPMS from disease onset (0.97 (0.96–0.98), $p < 0.0001$), and a longer treatment exposure during the RR phase (Q3 vs Q1: 0.66 (0.59–0.75), $p < 0.0001$) resulted significant protective factors against the accumulation of irreversible disability only in SPMS patients defined by the ND (Table 4).

Discussion

The currently used definition of SPMS course[1,2] is based on the subjective judgment of the treating neurologist who, retrospectively, defines SP as a history

of gradual progression following an initial RRMS course. This classification needs to be redefined[10] with the goal of developing more objective and data-driven SP definition that can facilitate communication between clinicians and between clinicians and MS patients, the comparisons of the results coming from natural history and prognostic studies, and the recruitment of more homogeneous populations for new clinical trials. Moreover, this consideration is even more relevant considering the current availability of therapeutic strategies for SPMS,[11] which showed to be able to slow the progression of the disease.

In this study, we evaluated the prevalence of SPMS using two definitions: one subjective based on ND and one more objective based on a DDA. The DDA identified a lower number of SPMS patients (12.1%) than the ND (20%). It is difficult to make a comparison with previous published data on the prevalence of the SPMS on cohorts from clinical databases and disease registries due to the lack of a homogeneous SP transition definition. However, in a previous study which involved 17,356 MS patients extracted from MSBase, the proportion of patients identified as SP by different DDAs and by the neurologists, varied from 13% to 19% (14% identified by the neurologists and 18% identified by the same algorithm applied in this study).[3]

Most important, we found that SPMS patients in DDA group were older, more disabled, and with a faster progression to severe disability, after the SP transition, in comparison with those diagnosed by the ND definition. This may be due to the fact that neurologists retrospectively assign the date of the conversion to SPMS at the time they suppose the positive slope of disability trajectory begins. In some instances, they can assign this event even if the EDSS score is between 0 and 4.0. The DDA instead is based on an objective algorithm that states that the minimum EDSS at the time of conversion to SPMS should be at least 4.0, thus excluding by definition all the "progression events" which start at an EDSS lower than 4.0. These findings suggest that the definition based on the DDA seems to capture more aggressive progressive patients.

Therefore, we used both SPMS groups for assessing the consistency and robustness of the major risk factors associated with the SP transition. Despite the differences in clinical and demographic features between the two SPMS cohorts, the Cox models, consistently demonstrated that an older age at onset, a multifocal onset, a higher baseline EDSS score, and a higher number of relapses are the most robust prognostic factors associated with a higher risk of SP conversion. It is noteworthy that both models showed a longer exposure to DMTs as the most important protective factor against the transition to SPMS. These results are in agreement with those from several previous studies that have tried to evaluate clinical and demographic factors associated with the onset of SPMS.[5–7,12–22]

Moreover, the results from more contemporary cohorts, in which patients were exposed to DMTs, have pointed out the impact of injectable DMTs in reducing the risk of conversion to SP.[23–26]

More recently, Brown et al.[27] have further analyzed the impact of DMT on the conversion to SPMS.

Their study aligns with our results: DMTs are shown to slow down the progression to the SP phase, and a longer exposure to therapy is indeed protective toward the conversion.[27]

Female gender and the time interval between disease onset and the first treatment start were associated with a lower risk of SPMS conversion in the group identified by the ND, but these factors were not confirmed in the model applied to the more aggressive SPMS cohort defined by the DDA.

In both cohorts, we have also evaluated the risk of reaching an irreversible EDSS 6.0 after the conversion to SPMS. The persistence of relapse activity and the EDSS score at SP conversion resulted in significant risk factors for subsequent disability accumulation. We did not find any effect of DMTs (>70% of the patients were receiving injectable DMTs) after the conversion to SPMS on the risk of reaching an irreversible EDSS 6.0 in both groups. This finding is in line with a previous work[28] in which the authors did not demonstrate any effect of DMT exposure on different measures of disability accumulation in 689 pairs of treated and untreated SPMS patients.[28]

Relapse activity before the conversion to SPMS, a longer time to convert to SPMS from disease onset, and a longer treatment exposure during the RR phase resulted significant protective factors against the accumulation of irreversible disability only in SPMS patients defined by ND, but they were not confirmed when used more stringent objective DDA criteria, suggesting that the accumulation of disability in more aggressive SPMS is at least partially independent of the events that occurred in the RR phase.

Some limitations of this study deserve discussion. First, the major limit of this multicenter study is the

lack of a systematic magnetic resonance imaging (MRI) acquisition and protocol analysis; thus, we did not include MRI in the model used to assess the risk of conversion to SPMS.

Second, the DDA is based uniquely on EDSS changes over time; therefore, all the limitations of the EDSS apply to our study: the EDSS relies deeply on lower limb function, being relatively low its sensitivity relative to upper limb function and cognitive changes in advanced MS. Moreover, by the inclusion a minimum of EDSS 4.0 in our DDA definition prevents to capture patients starting to progress early in the disease course, when permanent motor disability has not developed yet.

Third, although our results align with those provided from previous studies, the observational nature of our study design does not allow us to speak about a causative link between DMT exposure and SP conversion.

In conclusion, our study suggests that a more objective definition of SPMS based on a DDA is more reliable to identify patients with a more aggressive SP course in comparison with a retrospective subjective judgment of the treating neurologist. These findings can help to select more homogeneous population of SPMS patients to be included in future clinical trials or observational studies to evaluate the effect of DMTs during the SP phase of the disease.

Moreover, our results provide further insights on the most robust prognostic factors associated with the SPMS transition confirmed using different criteria of SPMS. It is noteworthy that the results also confirm the role of DMT exposure in reducing this risk, but not in preventing the disability accumulation after the transition to SPMS.

National MS registries, such as the IMSR, represent formidable tools to provide important information on the disease course and the effect of DMTs in the different phases of the disease.[9,29]

Declaration of Conflicting Interests

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